

### **AMENDMENTS TO THE CLAIMS**

The listing of claims will replace all prior versions, and listings, of claims in the application.

#### **Listing of Claims:**

1. (Original) A method of preparing a modified bone matrix comprising the steps of:  
providing a bone matrix; and  
exposing the bone matrix to a treatment or condition that increases at least one biological activity of the bone matrix.
2. (Withdrawn) The method of claim 1, wherein the exposing step increases the biological activity of the bone matrix so that undifferentiated mesenchymal cells treated with the bone matrix display increased expression of a marker indicative of osteoblastic or chondrocytic differentiation relative to cells treated with a control bone matrix.
3. (Withdrawn) The method of claim 2, wherein the marker is alkaline phosphatase.
4. (Withdrawn) The method of claim 2, wherein expression of the marker is within a factor of 2 relative to that induced by BMP-2.
5. (Withdrawn) The method of claim 2, wherein expression of the marker is increased by a factor of approximately 200-450 relative to expression induced by 10% fetal bovine serum.
6. (Withdrawn) The method of claim 2, wherein expression of the marker is increased by between 20 and 900-fold relative to expression induced by an inactivated bone matrix.
7. (Original) The method of claim 1, wherein the bone matrix is demineralized bone matrix derived at least in part from human bone.

8. (Original) The method of claim 1, wherein the biological activity is selected from the group consisting of: osteoinductive activity, osteogenic activity, chondrogenic activity, wound healing activity, neurogenic activity, contraction-inducing activity, mitosis-inducing activity, differentiation-inducing activity, chemotactic activity, angiogenic activity, vasculogenic activity, exocytosis-inducing activity, and endocytosis-inducing activity.
9. (Original) The method of claim 1, wherein the bone matrix comprises mineralized bone matrix, partially demineralized bone matrix, demineralized bone matrix, deorganified bone matrix, anorganic matrix, or a mixture thereof.
10. (Original) The method of claim 1, wherein the bone matrix comprises a mineralized, partially demineralized, demineralized, deorganified, or anorganic bone section.
11. (Withdrawn) The method of claim 1, wherein the exposing step comprises exposing the bone matrix to heat, cold, electromagnetic radiation, or ionizing radiation, or altering the pH of the bone matrix.
12. (Withdrawn) The method of claim 1, wherein the exposing step comprises contacting the bone matrix with a bioactive agent.
13. (Withdrawn) The method of claim 1, wherein the exposing step comprises contacting the bone matrix with a collagenase.
14. (Withdrawn) The method of claim 13, wherein the exposing step comprises contacting the bone matrix with an agent selected from the group consisting of: BMP-1, tolloid, furin, pepsin, trypsin, papain, and cathepsins.
15. (Withdrawn) The method of claim 1, wherein the method comprises the steps of: (a) contacting the bone matrix with a first agent that alters the structure of the bone matrix and (b) contacting the bone matrix with a second agent that cleaves or degrades a specific protein.

16. (Withdrawn) The method of claim 15, wherein the first agent cleaves or degrades collagen.
17. (Withdrawn) The method of claim 15, wherein the specific protein is a BMP inhibitor.
18. (Withdrawn) The method of claim 1, wherein the exposing step comprises contacting the bone matrix with a denaturing salt.
19. (Withdrawn) The method of claim 1, wherein the exposing step comprises contacting the bone matrix with LiCl.
20. (Withdrawn) The method of claim 1, wherein the treatment or condition activates a factor selected from the group consisting osteogenic factors, vascularizing factors, macrophage colony stimulating factor (MCSF), insulin-like growth factors (IGF), angiogenic factors, osteonectin, transforming growth factor (TGF), and bone morphogenic protein (BMP), and protein precursors of any of the foregoing factors.
21. (Withdrawn) The method of claim 1, wherein the treatment or condition degrades or inhibits an inhibitor of osteogenic or osteoinductive activity.
22. (Withdrawn) The method of claim 21, wherein the inhibitor is a BMP inhibitor or a cytokine.
23. (Withdrawn) The method of claim 22, wherein the inhibitor is selected from the group consisting of: noggin, chordin, gremlin, Dan, Cerberus, the protein related to Dan and Cerberus (PRDC), caronte, Dante, sclerostin, follistatin, follistatin-related gene (FLRG), ventroptin, and alpha-2 HS-glycoprotein.

24. (Withdrawn) The method of claim 1, wherein the exposing step comprises contacting the bone matrix with an antibody, wherein the antibody binds to an inhibitor of osteoinductive, osteogenic, or chondrogenic activity.

25. (Original) The method of claim 1, further comprising the step of adding to the bone matrix one or more bioactive agents selected from the group consisting of: small molecules, chemical compounds, cells, polynucleotides, proteins, protein fragments, peptides, drugs, viruses, antibiotics, anti-neoplastic agents, growth factors, hematopoietic factors, hormones, wound healing factors, and nutrients.

26. (Withdrawn) The method of claim 1, wherein the exposing step comprises contacting the bone matrix with a biological or chemical agent, and wherein the method further comprises the step of removing or inactivating residual agent.

27. (Original) The method of claim 1, further comprising the step of mixing the bone matrix with an agent selected from the group consisting of: carriers, stabilizing agents, diffusion barrier agents, and water reducing agents.

28. (Withdrawn) A method of treating a subject comprising the step of: implanting the bone matrix composition of claim 1 into a subject at a site of a bone or cartilage defect.

29. (Original) A method of producing a device for bone repair comprising the step of:  
providing a bone matrix prepared according to the method of claim 1, optionally including one or more additional components; and forming the device into a shape suitable for implantation into a subject, thereby producing an implantable device.

30. (Withdrawn) A method of treating a subject comprising the step of: implanting the device of claim 29 into a subject at a site of a bone defect.

31. (Original) A modified bone matrix comprising a bone matrix that has been exposed to a treatment or condition to produce a modified bone matrix, wherein the level of at least one biological activity of the modified bone matrix is increased relative to its level in a control bone matrix.

32. (Withdrawn) The modified bone matrix of claim 31, wherein undifferentiated mesenchymal cells treated with the modified bone matrix display increased expression of a marker indicative of osteoblastic or chondrocytic differentiation relative to cells treated with a control bone matrix.

33. (Withdrawn) The modified bone matrix of claim 31, wherein the marker is alkaline phosphatase.

34. (Withdrawn) The modified bone matrix of claim 31, wherein expression of the marker is within a factor of 2 relative to that induced by BMP-2.

35. (Withdrawn) The modified bone matrix of claim 31, wherein expression of the marker is increased by a factor of approximately 200-450 relative to expression induced by 10% fetal bovine serum.

36. (Withdrawn) The modified bone matrix of claim 31, wherein expression of the marker is increased by a factor of between approximately 20-900 relative to expression induced by an inactivated bone matrix.

37. (Original) The modified bone matrix of claim 31, wherein the bone matrix is demineralized bone matrix derived at least in part from human bone.

38. (Original) The modified bone matrix of claim 31, wherein the biological activity is selected from the group consisting of: osteoinductive activity, osteogenic activity, chondrogenic activity, wound healing activity, neurogenic activity, contraction-inducing activity, mitosis-

inducing activity, differentiation-inducing activity, chemotactic activity, angiogenic activity, vasculogenic activity, exocytosis-inducing activity, and endocytosis-inducing activity.

39. (Original) The modified bone matrix of claim 31, wherein the bone matrix comprises mineralized bone matrix, partially demineralized bone matrix, demineralized bone matrix, deorganified bone matrix, anorganic matrix, or a mixture thereof.

40. (Original) The modified bone matrix of claim 31, wherein the bone matrix comprises a mineralized, partially demineralized, demineralized, deorganified, or anorganic bone section.

41. (Original) The modified bone matrix of claim 31, further comprising one or more bioactive agents selected from the group consisting of: small molecules, chemical compounds, cells, polynucleotides, proteins, protein fragments, peptides, drugs, viruses, antibiotics, anti-neoplastic agents, growth factors, hematopoietic factors, hormones, wound healing factors, and nutrients.

42. (Original) The modified bone matrix of claim 31 further comprising an agent selected from the group consisting of: carriers, stabilizing agents, diffusion barrier agents, and water reducing agents.

43. (Withdrawn) The modified bone matrix of claim 31, wherein solubility of the modified bone matrix is greater than solubility of the unmodified bone matrix,

44. (Withdrawn) The modified bone matrix of claim 31, wherein one or more integrin binding sites is modified relative to an integrin binding site in a control bone matrix.

45. (Withdrawn) The modified bone matrix of claim 31, wherein the modified bone matrix has osteoinductive activity in a species in which the unmodified bone matrix is not osteoinductive.

46. (Withdrawn) The modified bone matrix of claim 45, wherein the species is selected from the group consisting of: dog, squirrel monkey, and human.

47. (Withdrawn) A method of treating a subject comprising the step of: implanting the modified bone matrix of claim 31 into a subject at a site of a bone or cartilage defect.

48. (Original) A device for bone repair comprising the modified bone matrix of claim 31, optionally including one or more additional components, formed into a device having a shape suitable for implantation into a subject.

49. (Withdrawn) A method of preparing a cell composition for implantation into a subject comprising steps of:

- obtaining a cell from a subject;
- culturing the cell in vitro;
- contacting the cell with the modified bone matrix of claim 31.

50. (Withdrawn) A method of treating a subject comprising the steps of:  
preparing a cell composition according to the method of claim 49; and  
implanting the cell composition into the subject.

51. (Withdrawn) A method of treating a subject comprising the steps of:  
preparing a cell composition according to the method of claim 49;  
deriving a tissue or organ from the cell composition; and  
implanting the tissue or organ into the subject.

52. (Withdrawn) A cell composition prepared according to the method of claim 49.

53. (Withdrawn) A tissue or organ derived in vitro from the cell composition of claim 52.

54. (Withdrawn) A modified bone matrix comprising a collagen-containing bone matrix, wherein at least a portion of the collagen is cleaved or degraded.
55. (Withdrawn) The modified bone matrix of claim 54, wherein at least 10%, at least 25%, at least 50%, at least 75%, or at least 90% of the collagen is cleaved or degraded.
56. (Withdrawn) The modified bone matrix of claim 54, wherein at least a portion of the collagen is present as collagen fragments.
57. (Withdrawn) The modified bone matrix of claim 56, wherein at least 10%, at least 25%, at least 50%, at least 75%, or at least 90% of the collagen is present as collagen fragments.
58. (Withdrawn) The modified bone matrix of claim 54, wherein the level of at least one biological activity of the modified bone matrix is increased relative to its level in a control bone matrix.
59. (Withdrawn) A method of treating a subject comprising the step of: implanting the modified bone matrix of claim 54 into a subject at a site of a bone or cartilage defect.
60. (Withdrawn) A device for bone repair comprising the modified bone matrix of claim 54, optionally including one or more additional components, formed into a device having a shape suitable for implantation into a subject.
61. (Withdrawn) A modified bone matrix comprising a collagen-containing bone matrix, wherein at least a portion of an inhibitor of osteoinductive, osteogenic, or chondrogenic activity is cleaved or degraded.
62. (Withdrawn) The modified bone matrix of claim 61 wherein at least 10%, at least 25%, at least 50%, at least 75%, or at least 90% of the inhibitor is cleaved or degraded.



63. (Withdrawn) The modified bone matrix of claim 54, wherein at least a portion of an inhibitor of osteoinductive, osteogenic, or chondrogenic activity is cleaved or degraded.

64. (Withdrawn) A method of treating a subject comprising the step of: implanting the modified bone matrix of claim 61 into a subject at a site of a bone or cartilage defect.

65. (Withdrawn) A device for bone repair comprising the modified bone matrix of claim 61, optionally including one or more additional components, formed into a device having a shape suitable for implantation into a subject.

66. (Withdrawn) A human DBM composition exhibiting increased solubility in an aqueous medium compared to that of a standard DBM composition.

67. (Withdrawn) The human DBM composition of claim 66, wherein the medium is at physiological conditions.

68. (Withdrawn) The human DBM composition of claim 66, wherein the medium is tissue culture medium.

69. (Withdrawn) The human DBM composition of claim 66, wherein the solubility of the human DBM composition is greater than that of a standard DBM composition by between 10% and 4000% percent.

70. (Withdrawn) A human DBM composition exhibiting greater solubility in rat muscle compared to that of a standard DBM composition.

71. (Withdrawn) The human DBM composition of claim 70, wherein implantation of the DBM compositions results in a residual area of DBM within the rat muscle, and wherein the area occupied by the human DBM composition divided by the area occupied by a standard DBM composition is less than or equal to 0.9 as determined after a period of time.

72. (Withdrawn) A method for preparing a human DBM composition comprising the step of exposing human DBM to a treatment or condition that increases the solubility of the human DBM, wherein the DBM exhibits increased solubility in vitro, in vivo, or both in vitro and in vivo, and wherein the human DBM composition has increased biological activity relative to a standard DBM composition.